REMARKS

Prior to the present amendment, claims 42-50 were pending in the application. Claims 45, 47, and 49 have now been canceled, without prejudice. New claims 51-59 have been added, and specify methods of inhibiting Aβ fibril formation (claims 51-55) and preventing or treating Alzheimer's disease (claims 56-59) by administration of peptides including the seven particular sequences that are also listed in claims 42 and 43. No new matter is added by the amendments.

In the Advisory Action mailed on February 15, 2007, the Examiner maintains the prior made rejection under 35 U.S.C. § 112, first paragraph, stating "there is no consensus that any compound that is capable of binding to amyloid peptide is similarly capable of inhibiting amyloid peptide aggregation, and [the] specification does not provide support that the particular peptides, as now claimed, do indeed inhibit amyloid peptide polymerization."

In response, Applicants first note that they are not claiming "any compound" that binds to amyloid peptide. Rather, the peptides claimed by Applicants are based on a sequence that has been shown to be critical for amyloid peptide polymerization. Importantly, the blocking of this sequence by peptide binding has been shown to block amyloid peptide polymerization.

Applicants further submit that it is understood in the art that binding to amyloid peptide, particularly in a region required for polymerization, indicates inhibition of amyloid polymerization. No evidence has been made of record providing an indication to the contrary.

Each of these points is addressed in further detail, as follows.

The present invention is based on the discovery that the sequence KLVFF of amyloid β is important for amyloid β polymerization. In Example 1 of the present application, Applicants showed that peptides in the region of amyloid β corresponding to KLVFF (16-21) specifically

bind to amyloid β with higher affinity than sequences from most other regions of the protein (also see Fig. 2A and Fig. 2B). Based on this discovery, a mutational analysis of a KLFVV-containing peptide was carried out. As is shown in Example 2, when amyloid β 1-28, which is normally capable of forming fibrils, was subjected to mutagenesis in the KLVFF sequence of the peptide, it lost the ability to form fibrils. Further showing the importance of this region, Example 3 shows that fibrils did not form when amyloid β was co-incubated with a peptide including the sequence KLVFF under conditions that would otherwise result in amyloid β polymerization.

The experiments described above show clearly that binding of a peptide to amyloid β correlates with the ability of the peptide to inhibit fibril formation. The peptides of the present claims are in the same region of amyloid β that was tested in these experiments, as they either completely encompass the sequence KLVFF (HHQKLVFFAE and VHHQKLVFFA) or overlap substantially with this sequence (HQKLVF; HHQKLVF; VHHQKLVF; YEVHHQKLVF; and GYEVHHQKLV). Further, each of these peptides was shown to bind to amyloid β (see, e.g., Fig. 2A and Fig. 2B).

The application itself thus provides very strong evidence supporting Applicants' position that the peptides of the present claims inhibit fibril formation, and no evidence has been presented to the contrary.

Support for the present Applicants' position also is present in the art. For example, results following up on the experiments described in the present application were published in a paper by Tjernberg et al., J. Biol. Chem. 272(19):12601-12605, 1997 (a copy is enclosed). In this paper, studies were carried out confirming that peptides including the sequence KLVFF bind to the homologous sequence in Aβ (i.e., Aβ 16-20). In addition, combinatorial pentapeptide

libraries were screened to identify additional peptides that bind to KLVFF. Two peptides identified in this manner were tested in anti-fibrillation assays and were found to block the formation of Aβ fibrils, as compared to a non-binding peptide control (page 12603, right column). These experiments thus provide additional support for a correlation between binding to Aβ and inhibition of fibril formation, for peptides directed to the KLVFF region of Aβ. Further, this peer-reviewed publication concludes with the following statement.

> The overall conclusion from these studies is that not only the KLVFF peptide (Aβ16-20) but also structurally different peptides consisting of non-natural amino acids have the capability of binding Aβ and preventing its assembly into amyloid fibrils. Therefore, it is reasonable to assume that pharmacologically useful organic non-peptide molecules with similar functional properties as the present ligands can be synthesized." (Emphasis added.)

If those of skill in the art did not think that such a conclusion was reasonable, based on the data, then they would not have permitted the inclusion of this statement in the paper. This shows that those of skill in the art, similar to the present Applicants, understand that in the region of KLVFFA there is a strong correlation between the ability of an agent to bind to amyloid β and the ability of the agent to inhibit amyloid β fibril formation.

Additional support for Applicants' position can be found, for example, in Findeis et al., Biochemistry 38:6791-6800, 1999 (a copy is enclosed). This peer-reviewed paper describes the characterization of peptide-based inhibitors of amyloid β polymerization. In the abstract, the authors state: "The intrinsic affinity of Aβ for itself suggested that Aβ-specific interactions could be adapted to the development of compounds that would bind to Aβ and prevent it from polymerizing." Further in the abstract, showing that the above-noted suggestion has indeed been found to be true, the authors note "Aβ-derived peptides of fifteen residues were found to be

inhibitory of Aβ polymerization."

Further support can be found in U.S. Patent No. 6,303,567 (and other patents in this family), which include data showing that peptides based on the so-called "Aβ aggregation core domain" (defined by this group as amino acids 17-21) inhibit Aβ aggregation of natural β-amyloid (see, e.g., Example 3 of the '567 patent).

In view of the above, Applicants submit that the present claims, which focus on seven specific peptide sequences, meet the requirements of the written description requirement of 35 U.S.C. § 112, first paragraph. The prior made rejection of the claims in this case on this basis should therefore be withdrawn and the claims allowed.

Applicants further request clarification as to the designation of the rejection as a "new matter" rejection. The claims do not include new matter, as the presently claimed methods are clearly described in the application. Further, as is stated in M.P.E.P. § 2163.07, "amendments to an application which are supported in the original description are NOT new matter." (Emphasis in original.) Examples of support for claims 42-50, with respect to the use of the peptides of these claims in the inhibition of amyloid β peptide polymerization (both in vitro and in vivo), were provided in the Reply filed on January 16, 2007. These Examples are provided again, below, for the Examiner's convenience.

Figures 2A and 2B

These figures show the binding of different amyloid β peptides to Aβ 1-40. For example, results obtained with peptides 12-21 and 13-22 (as specified in the present claims) are provided in Figure 2A. As is made clear in the passages of the specification set forth below, binding of

peptides to Aβ 1-40 correlates with the inhibition of Aβ polymerization.

Page 1, lines 10-15:

"The present invention relates to compounds, which are of special interest by their ability to bind to the KLVFF-sequence in the peptide amyloid β and to **inhibit polymerization** of the amyloid β peptide." (Emphasis added.)

Page 3, lines 20-37:

"It was assumed that ligands which bind to recognition sequences would be capable of **inhibiting Aβ polymerization** and possibly also dissolve preformed Aβ polymers *in situ*. The strategy in finding such Aβ ligands was to identify critical binding regions in Aβ and, based on their sequences, develop a compound capable of blocking the Aβ-Aβ binding.

According to the invention, it was hypothesized that compounds capable of binding to regions in the Aβ-molecule critical for its polymerization might **inhibit amyloid fibril formation**, as described in more detail below.

According to the invention, it has now been found that **the Lys-Leu-Val-Phe-Phe (KLVFF) sequence in Aβ is necessary for polymerization to occur. Peptides incorporating this sequence bind to Aβ and are capable of blocking the fibril formation of Aβ-1-40 and are therefore potentially useful as drugs**." (Emphasis added.)

Page 4, lines 9-15:

"Thus, it was concluded that the Lys-Leu-Val-Phe-Phe (16-20) motif serves as a

structural basis for the development of peptide and non-peptide agents aimed at **inhibiting amyloidogenesis *in vivo***. This is a novel finding and the compounds are of utmost interest as being useful as drugs for Alzheimer's disease." (Emphasis added.)

Page 6, lines 1-3:

"In a preferred embodiment of the present invention, the compound exhibits an ability to **inhibit polymerization of amyloid β** peptide." (Emphasis added.)

Page 8, lines 12-24:

"Also claimed is the use of a compound, preferably of the formula (I) or (II), which is able to bind to the KLVFF-sequence in amyloid β peptide and which has the ability to **inhibit polymerization of amyloid β** peptide, for the manufacture of a medicament for the treatment or prevention of amyloidosis, especially in the treatment or prevention of Alzheimer's disease associated with amyloidosis, for the treatment or prevention of demens in patients with Down's syndrome, for the treatment or prevention of Hereditary cerebral hemorrhage with amyloidosis (Dutch type) or for the prevention of fibril formation of human amyloid protein." (Emphasis added.)

Page 14, lines 22-24:

"Like KLVFF, the D-amino acid ligands were found not only to bind to Aβ but also to **inhibit amyloid fibril formation**." (Emphasis added.)

Page 14, lines 27-33:

"The results further indicate that KLVFF will be useful in the identification of small organic molecules (e.g. by screening of substance libraries) with the ability to bind to Aβ in this relevant region and **inhibit amyloid fibril formation** (candidate drugs for the treatment of Alzheimer disease and other related amyloidoses)." (Emphasis added.)

Page 15, lines 31-36:

"Hence, a molecule capable of binding to a site in the Aβ molecule that is critical for **fibril formation** with an affinity higher that native Aβ should have reasonable chances to inhibit amyloid growth and maybe also specifically dissolve amyloid fibrils." (Emphasis added.)

Page 16, lines 1-6:

"In conclusion, we have identified an Aβ sequence, KLVFF, which is required for **amyloid fibril formation**. The KLVFF peptide may serve as a model substance for the synthesis of non-peptide Aβ-ligands that **interfere with the polymerization of Aβ** molecules." (Emphasis added.)

Page 16, lines 14-22:

"It was also demonstrated that short peptides incorporating Aβ-16-20 can function as ligands that bind to Aβ and **inhibit the formation of amyloid fibrils**. Since these peptide ligands are relatively small, they are amenable for identification of other organic molecules with similar functional properties. Non-peptide homologues of KLVFF should be useful as pharmacological

drugs for the treatment of Alzheimer's disease in the future." (Emphasis added.)

Information Disclosure Statement

Applicants finally note that the Form PTO 1449 that was submitted with an Information Disclosure Statement filed on November 26, 2003 and returned in the Office Action February 15, 2006, has not been fully initialed. Specifically, Applicants respectfully request confirmation that the documents listed under the section 'Foreign Patent Documents' were considered, and that the Form PTO 1449 be initialed with respect to the foreign patent documents and returned to us.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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